Catalytic Asymmetric Cross-Couplings of Racemic α-Bromoketones with Arylzinc Reagents[**]

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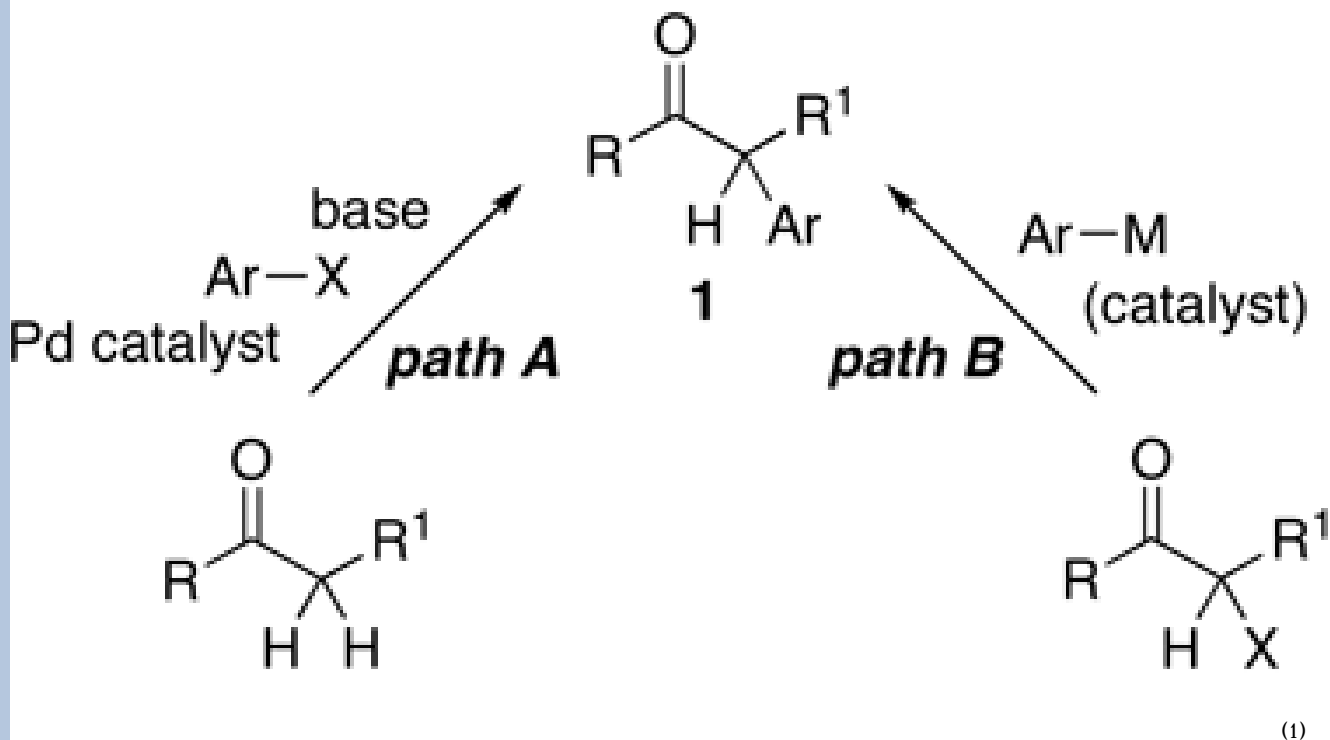
Keywords

Because an array of interesting target molecules include ketones that bear an α-aryl substituent, the development of methods for the synthesis of this structural motif has been an active area of investigation.[1] For example, extensive effort has recently been devoted to the discovery of palladium catalysts for the cross-coupling of ketones with aryl halides in the presence of a Brønsted base (path A in eq 1; via an enolate).[2] Furthermore, in the case of α, α-disubstituted ketones, catalytic asymmetric α-arylations have been described wherein quaternary stereocenters are generated with excellent enantioselectivity.[3,4] Unfortunately, these methods cannot be applied to the asymmetric synthesis of more commonly encountered tertiary stereocenters, due to the propensity of α-arylketones such as **1** to enolize under the reaction conditions.[5,6]
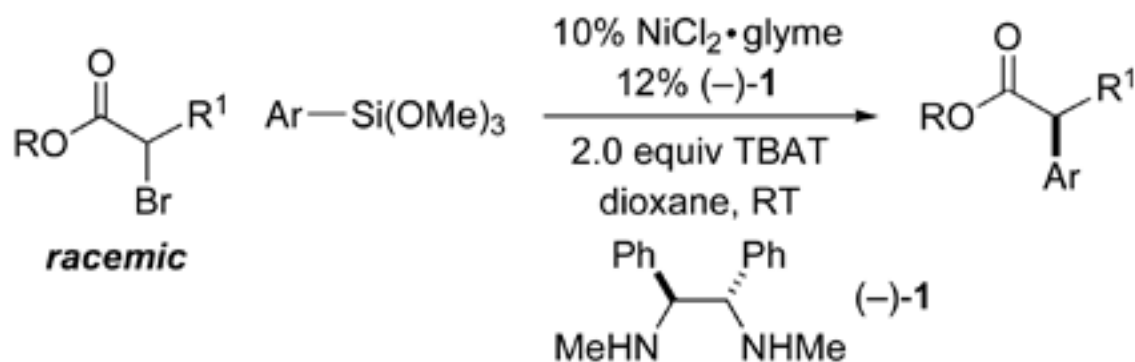
$$R-\overset{\displaystyle O}{\underset{}{C}}-\overset{R^1}{\underset{H\ Ar}{C}}$$

1

path A

base
Ar—X
Pd catalyst

$$R-\overset{\displaystyle O}{\underset{}{C}}-\overset{R^1}{\underset{H\ H}{C}}$$

path B

Ar—M
(catalyst)

$$R-\overset{\displaystyle O}{\underset{}{C}}-\overset{R^1}{\underset{H\ X}{C}}$$

(1)

Alternatively, an umpolung arylation process, whereby a ketone that bears an α leaving group reacts with an arylmetal reagent, could provide the target α-arylketone (path B in eq 1). Until recently, there were no examples of palladium- or nickel-catalyzed cross-couplings between secondary α-halocarbonyl compounds and arylmetals (metal = B, Si, Sn, or Zn). In 2007, we reported that a nickel catalyst can achieve Hiyama arylation reactions with a wide array of electrophiles, including secondary α-halocarbonyl compounds (and Lei later described a nickel-based method for Suzuki couplings).[7] In the case of α-haloesters, we were able to subsequently develop a catalytic asymmetric α-arylation process that furnishes tertiary stereocenters (eq 2; TBAT = $[F_2SiPh_3]^-[NBu_4]$).[8] However, we could not apply this method to corresponding Hiyama arylations of α-haloketones, presumably due to the Brønsted-basic reaction conditions.[9,10]

$$RO-\overset{\displaystyle O}{\underset{}{C}}-\overset{R^1}{\underset{Br}{C}} \quad Ar-Si(OMe)_3 \xrightarrow[\substack{\text{2.0 equiv TBAT} \\ \text{dioxane, RT}}]{\substack{10\% \ NiCl_2\cdot glyme \\ 12\% \ (-)\text{-}1}} RO-\overset{\displaystyle O}{\underset{}{C}}-\overset{R^1}{\underset{Ar}{C}}$$

racemic

$$\overset{\text{Ph}\qquad\text{Ph}}{\underset{\text{MeHN}\qquad\text{NHMe}}{C-C}} \quad (-)\text{-}1$$

(2)

Unlike cross-coupling processes such as the Hiyama and Suzuki reactions, which often employ Lewis/Brønsted-basic activators, the Negishi reaction typically proceeds without an additive, [11,12] thereby making it an attractive starting point for the development of a method for the catalytic asymmetric α-arylation of ketones to generate (potentially labile) tertiary stereocenters. In this report, we establish that a nickel/pybox catalyst can indeed achieve enantioselective cross-couplings of racemic α-bromoketones with arylzinc reagents under very mild conditions in good ee and yield (eq3).[13,14]
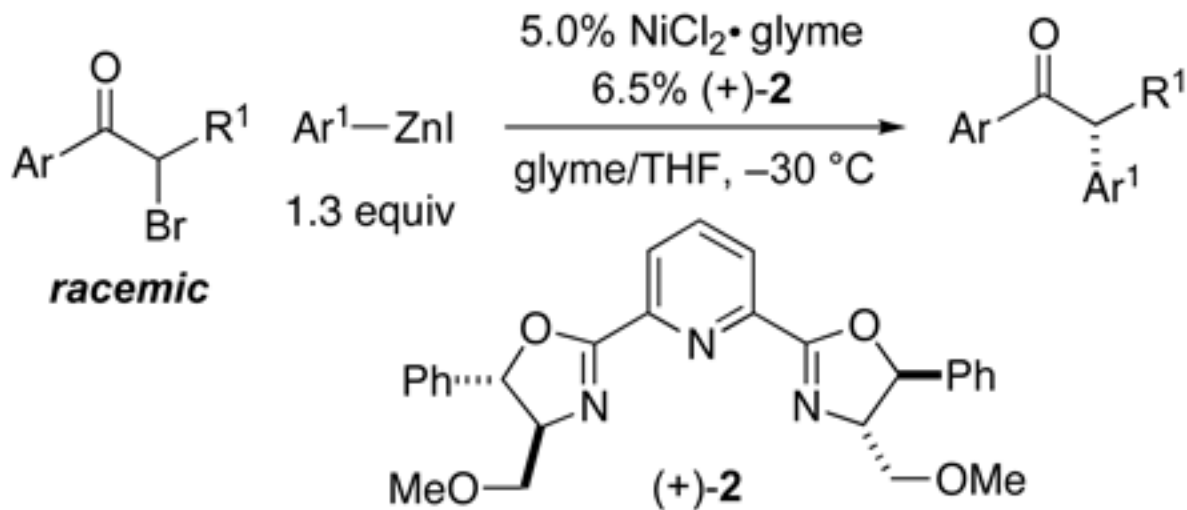
(3)

The data in Table 1 illustrate the role that various reaction parameters play in determining the efficiency of this stereoconvergent Negishi α-arylation of ketones. Thus, no cross-coupling occurs if NiCl$_2$·glyme is omitted (Table 1, entry 2), whereas carbon-carbon bond formation does proceed in the absence of ligand **2**[15] (Table 1, entry 3). Pybox ligands other than **2** furnish lower ee and yield (Table 1, entries 4 and 5), as do solvents other than a glyme/THF mixture (Table 1, entries 6–8). At room temperature, the catalyst system is somewhat less effective than at −30 °C (Table 1, entry 9).

With our optimized method, we can achieve Negishi cross-couplings of racemic 2-bromopropiophenone with an array of arylzinc reagents in excellent ee and good yield (Table 2)[16] although the efficiency of the process is sensitive to the steric demand of the nucleophile (Table 2, entry 2). The organozinc can include a range of functional groups, such as OR, halogen, NR$_2$, and SR. Diarylzinc reagents (Ar$_2$Zn) and arylzinc iodides (ArZnI) generally furnish similar enantioselectivities and yields (e.g., Table 2, entry 1)[17] The α-arylated ketone is stable to racemization under these conditions.

Z-pybox
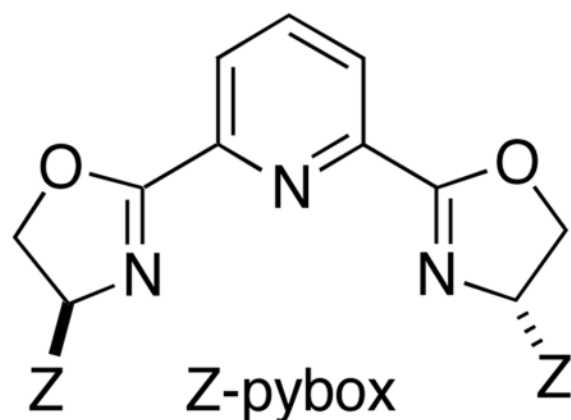
We have examined the scope of this method for the catalytic asymmetric α-arylation of ketones not only with respect to the nucleophile (Table 2), but also the electrophile (Table 3). Very good ee's and useful yields are observed with a variety of α-alkyl substituents, including those that are functionalized (Table 3, entries 2 and 3) and β-branched (Table 3, entry 4); however, if R is large, little of the cross-coupling product is formed (Table 3, entry 5). If the aryl group of the ketone is bulky, the reaction proceeds with moderate enantioselectivity (Table 3, entries 6 and 7). On the other hand, good ee's are observed regardless of whether the group is electron-rich (Table 3, entry 8) or electron-poor (Table 3, entry 9). A thiophene is compatible with this nickel-based coupling process (Table 3, entry 10).[18]

In conclusion, we have developed the first catalytic asymmetric method for cross-coupling arylmetal reagents with α-haloketones, specifically, the $NiCl_2 \cdot glyme$/**2**-catalyzed reaction of arylzincs with racemic secondary α-bromoketones. This stereoconvergent carbon–carbon bond-forming process occurs under unusually mild conditions (−30 °C and no activators), thereby allowing the generation of potentially labile tertiary stereocenters. Ongoing efforts are directed at further expanding the scope of cross-coupling reactions of alkyl electrophiles.

Experimental Section

General Procedure

A solution of the arylmagnesium bromide (1.6 mmol; 1.6 equiv) was added to a solution of ZnI_2 (510 mg, 1.6 mmol; 1.6 equiv) in THF (final concentration of ArZnI = 0.20 M) under argon. The mixture was stirred for 40 min at room temperature (a precipitate is immediately observed), and then it was cooled to −30 °C. $NiCl_2 \cdot glyme$ (11.0 mg, 0.050 mmol; 0.050 equiv) and (+)-**2** (29.9 mg, 0.065 mmol; 0.065 equiv) were added to an oven-dried 50-mL flask. The flask was purged with argon, and the α-bromoketone (1.0 mmol; 1.0 equiv) was added, followed by glyme (13.5 mL). This solution was allowed to stir at room temperature for 20 min, and then it was cooled to −30 °C. The suspension of ArZnI (6.5 mL, 1.3 mmol; 1.3 equiv) was added dropwise over 3 min, and the reaction mixture was stirred at −30 °C for 4 h. Then, the reaction was quenched with saturated ammonium chloride (10 mL). The reaction mixture was diluted with Et_2O (50 mL), washed with distilled water (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. The product was purified by flash chromatography.

References

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2. For overviews, see: a) Reference 1; Culkin DA, Hartwig JF. Acc Chem Res 2003;36:234–245. [PubMed: 12693921]

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6. For examples of methods for the asymmetric synthesis of cyclic α-arylketones wherein the α carbon is a tertiary stereocenter, see: a) Cheon CH, Yamamoto H. J Am Chem Soc 2008;130:9246–9247. [PubMed: 18582053] b) Aggarwal VK, Olofsson B. Angew Chem 2005;117:5652–5655.Angew Chem, Int Ed 2005;44:5516–5519. c) Shen Y-M, Wang B, Shi Y. Angew Chem 2006;118:1457–1460.Angew Chem, Int Ed 2006;45:1429–1432. d) Soorukram D, Knochel P. Angew Chem 2006;118:3768–3771.Angew Chem, Int Ed 2006;45:3686–3689.

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8. Dai X, Strotman NA, Fu GC. J Am Chem Soc 2008;130:3302–3303. [PubMed: 18302392]

9. We believe that, in certain cases, even the product of the Hiyama arylation illustrated in eq 2 may be susceptible to racemization (e.g., with Ar = 4-$(F_3C)C_6H_4$; see footnote 7a of Reference 8).

10. For asymmetric Negishi alkylations of α-haloamides, see: Fischer C, Fu GC. J Am Chem Soc 2005;127:4594–4595. [PubMed: 15796523]

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14. For a recent overview of asymmetric cross-couplings of secondary alkyl electrophiles, see: Glorius F. Angew Chem, Int Ed. in press

15. Ligand 2 can be synthesized in one or two steps from a commercially available amino alcohol and a commercially available pyridine derivative (see the Supporting Information).

16. Notes: a) In preliminary studies under our standard conditions, α-chloroketones and heteroarylzinc reagents have not been suitable substrates (low yield and/or ee); b) During the course of the cross-coupling, the ee of the unreacted α-bromoketone is <5%, and the ee of the product is essentially constant.

17. Notes: a) The use of less than 1.1 equivalent of Ar_2Zn (⇒2.2 equiv of the Ar group) leads to significantly lower yields. Therefore, we generally employ ArZnI (1.3 equiv) as the arylating agent; b) We prepare ArZnI by the reaction of a Grignard reagent with ZnI_2. In preliminary experiments, we have observed that arylzinc halides produced by zinc insertion into aryl halides may also be employed, whereas the use of commercially available arylzinc halides leads to lower yields.

18. In a preliminary study, we obtained 72% ee and 68% yield in a Negishi phenylation of racemic 2-bromocyclohexanone. To the best of our knowledge, there has been no previous report of a catalytic asymmetric arylation of a dialkylketone (see References 3 and 4).

Table 1

Catalytic asymmetric arylations of racemic α-bromoketones: Effect of reaction parameters

entry	variation from the "standard" conditions	ee (%)	yield (%)[a]
1	none	94	87
2	no NiCl$_2$·glyme	-	<5
3	no (+)-**2**	-	55
4	Ph-pybox, instead of (+)-**2**	71	54
5	*i*-Pr-pybox, instead of (+)-**2**	73	6
6	glyme only	-	<5
7	THF only	87	52
8	DMF, instead of glyme/THF	-	<5
9	r.t.	89	81

[a]The yield was determined by GC versus a calibrated internal standard.

Table 2

Catalytic asymmetric arylations of racemic α-bromoketones: Variation of the nucleophile

entry	Ar	ee (%)	yield (%)^a
1	Ph	96(95^b)	86 (88^b)
2	2-(MeO)C$_6$H$_4$	-	<5
3	3-MeC$_6$H$_4$	94	88
4^b	3-(MeO)C$_6$H$_4$	94	87
5	4-FC$_6$H$_4$	96	74
6	4-(MeO)C$_6$H$_4$	96	93
7	4-(Me$_2$N)C$_6$H$_4$	93	85
8	4-(MeS)C$_6$H$_4$	96	71

All data are the average of two experiments.

^{a}Yield of purified product.

^{b}Ar$_2$Zn (1.1 equiv) was used, rather than ArZnI.

Table 3

Catalytic asymmetric arylations of racemic α-bromoketones: Variation of the electrophile

entry	Ar	R	ee (%)	yield (%)^a
1	Ph	Et	94	86
2	Ph	CH$_2$Ph	95	76
3^b	Ph	CH$_2$CH$_2$Cl	92	90
4^c	Ph	iBu	95	89
5	Ph	iPr	-	<5
6	2-FC$_6$H$_4$	Me	72	80
7^b	2-(Et)C$_6$H$_4$	Me	75	79
8	4-(MeO)C$_6$H$_4$	Me	96	90
9	4-(F$_3$C)C$_6$H$_4$	Me	87 (89^c)	76(82^c)
10	2-thienyl	Me	96	81

All data are the average of two experiments.

^{a}Yield of purified product.

^{b}Run at −20 °C.

^{c}Ar$_2$Zn (1.1 equiv) was used, rather than ArZnI.